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The impact of HIV on 30-day survival amongst patients undergoing cardiac surgery at Groote Schuur Hospital in the ART era

Dissertation for the degree of

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Declaration

I, …Linda Boloko……., hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Introduction: The impact of HIV on the one-month perioperative morbidity and mortality in patients undergoing cardiac surgery in sub-Saharan Africa (SSA) in the Anti-Retroviral Therapy (ART) era is not known. Pre ART era data from South Africa suggested that patients with a CD4 count less than 400 should be selected with caution. European and North American information suggest that short and long-term outcomes of cardiac surgery in patients with HIV on ART are acceptable, but this experience cannot be generalized to the SSA where demographic profiles, co-morbidities and underlying cardiac pathology requiring surgery is significantly different.

Methods: We set out to conduct a retrospective review of the Groote Schuur Hospital and Chris Barnard Division of Cardiothoracic Surgery patient records between 2003 and 2013, to evaluate the perioperative and one month outcomes of HIV positive patients undergoing cardiac surgery at our tertiary care institution. Eighty-one patients met all our study inclusion criteria.

Findings: The patient cohort were young, (mean age 34), female (73%) and predominantly black (83%), 41% were on ART, 28% had previous tuberculosis and the average CD4 count was 426.5 cells/μL. Of the 81 patients 54 (67%) underwent valve surgery, 5 (6%) underwent CABG and 3 (4%) had both. Five (6%) patients died in hospital prior to discharge. Bleeding requiring transfusion was the most common complication (n=14; 17.3%) with 2 (2.5%) requiring relook. Other complications included wound sepsis in 9 (11%), complete heart block in 5 (6%), acute kidney injury in 4 (5%), hospital-acquired pneumonia in 3 (4%), cardiac tamponade in 3 (4%) and only one (1%) needlestick injury was reported. The predictors of death included the need for aortic root replacement and prolonged cardiopulmonary bypass time (OR 25 [p=0.006] and OR 1.02 [p= 0.01] respectively)

Conclusion: HIV positive patients had cardiac surgical outcomes with low mortality rates comparable to international trends which were independent of CD4 counts. Perioperative complications rates were slightly higher than anticipated.

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Abbreviations

AIDS = Acquired Immunodeficiency Syndrome

ART = antiretroviral therapy

AVR = aortic valve replacement

AKI = acute kidney injury

CABG = coronary artery bypass graft

CAD = coronary artery disease

CD4 = cluster of differentiation 4

CHB = complete heart block

DVR = double valve replacement

eGFR = electronic glomerular filtration rate

HIV = human immunodeficiency virus

IE = infective endocarditis

H. Influenzae =Haemophilus Influenzae

LVEF = left ventricular ejection fraction

MVR = mitral valve replacement

NYHA = New York Heart Association

S. Aureus = Staphylococcus Aureus

TB = tuberculosis

SECTION A: Literature Review

Objectives

The objectives of the literature review were to appraise published literature in order to:

- Review the historic and current outcomes of HIV positive patients undergoing cardiac surgery
- Review literature in sub-Saharan Africa on the outcomes of HIV positive patients undergoing cardiac surgery
- Review the impact of HIV on outcomes of patients undergoing cardiac surgery

Search strategy

We used several databases including PubMed/MEDLINE, Scopus and Google Scholar to find articles in this topic which have been published. These databases are fully available through the University of Cape Town online library support. The search terms used included 'cardiac surgery and HIV', 'HIV cardiac surgery and outcomes', 'valve surgery and HIV', 'Coronary artery bypass graft and HIV'. The results were not limited to any time period but predominantly articles from 1990's to 2014 were found. There was no limitation to studies from any particular continent. Only studies published in the English language were reviewed. Upon reading the article, the references used by the publication itself were studied and similar articles searched for using the publication title. The articles would then be imported to Endnote X9.2 referencing manager which would then be used as a citation manager.

Ten studies were found looking at valve and/or coronary artery bypass grafting in the HIV positive population. One study which was not included reviewed heart transplantation in HIV positive patients. Several supporting articles were found with subsequent reading. These included topics around antiretroviral therapy (ART) and coronary artery disease, prevalence of HIV in South Africa, prevalence and burdens of Rheumatic Heart Disease (RHD).

Background

A South African National HIV survey in 2012 estimated that 6.4 million (12.2%) people were HIV positive, an increase from 5.2 million (10.6%) in 2008. This epidemiological curve shift was presumed to be a result of the effects of increased ART coverage.[1] This has led to HIV becoming a chronic disease with almost a normal life expectancy. HIV positive patients are presenting more often for cardiac surgery for disease related to the HIV itself and treatment thereof and to traditional cardiac disease unrelated to HIV.[2, 3] Sub-Saharan Africa (SSA) has a high burden of RHD with more patients operated for valve replacement surgery including those with infective endocarditis.

HIV itself is a risk factor for development of acute coronary syndromes through endothelial dysfunction, heightened pro-inflammatory state, dyslipidemia and thrombosis; all these events related to chronic immune activation prior to ART initiation.[4, 5] Although ART reduces viral replication, immune activation, and markers of coagulation, these indices do not normalize and patients are still at risk of arterial thrombosis.[6] Furthermore, protease inhibitors (PI) have a potential to cause metabolic disturbances including insulin resistance, dyslipidaemia therefore contributing to development of coronary artery disease alongside or in the absence of traditional risk factors. On the other hand, relationship of non-nucleoside reverse transcriptase inhibitors (NNRTI) and risk myocardial infarction has been accounted to combination therapy with PI rather than NNRTI having independent significant effect. All these relationships are time dependent, the longer the duration of ART use, the higher the risk.

Current trends in cardiac surgery

One of the earliest studies done in the research of outcomes of HIV positive patients undergoing cardiac surgery was by Trachoitis et al.[7] This was a small sample of 37 patients with mean age 41, most patients were on ART at the time of the surgery with preserved CD4 T lymphocytes (CD4 count) and no acquired immunodeficiency

syndrome (AIDS) defining opportunistic infections. In this study, a larger group of 27 patients, mean age 43 had coronary artery bypass graft (CABG) while the other 10 patients, mean age 38 had valve surgery. The group that underwent valve surgery were mostly fit young patients who were drug users presenting with bacterial endocarditis, only one early death was reported due to sepsis in the valve group. This study highlights the trend that more HIV positive in stable chronic disease are presenting more for revascularization than valve surgery as a result of bacterial endocarditis.

Subsequent follow-up showed that 81% were free from angina or failure symptoms, myocardial infarction, death and repeat revascularization; this is inclusive of both the CABG and the valve patients. This data is encouraging on the long term outcome and low early mortality rates in this population. In a setting like South Africa where there's a high burden of RHD, valve surgery is still a common indication for surgery in this population group.

However, Mestres et al did a review of younger patients mean age 34 who had undergone cardiac surgery with 80% of patients being drug addicts and majority presenting as a result of acute infective endocarditis (IE) with an early mortality rate of 23%.[8] This mortality was associated with emergency operations as a result of unstable clinical status.

In contrast, Chong et al had no early hospital mortality for the in their review of 22 patients who underwent valve surgery for bacterial endocarditis.[9] These were younger patients in good physical status with no other comorbidities. There was however poor long-term outcome which was mostly related to continued intravenous drug addiction with resultant recurrence of bacterial endocarditis with new organism.
Table 1 shows current studies around this topic and their findings.

Table 1: Selected studies to date

Year	*Study*	*Mean Age*	*Patients (n)*	*CABG (n)*	*Valve (n)*	*Valve+CABG (n)*	*Early Mortality (%)*	*Complications (%)*	*Survival (%)*		
									1 year	***3 years***	***5 years***
1985-2002	Mestres	34	31	5	26	-	23	19	65	42	
1990-1999	Chong	38	22	-	22		0	14			40
1994-2000	Trachoitis	41	37	27	8	2	2.7	38	81		
1995-2003	Blyth	33	49	3	45		6	35	-	-	-
1997-2005	Boccara	47vs50	27vs54	27vs54	0	-	0			41	
1998-2004	Filsoufi	47	25	7	13	2	4	20	92	86	-
1998-2006	Castillo	49	39	12	17	5	5	25	91	86	81
2004-2007	Nel	32	17	-	6	-	0		83		
1998-2009	Robich	49	9771	3713	1563		7.2	38	-	-	-
2000-2010	Polanco	52	1239	789	450		2.6	-	-	-	-

Like all forms of surgery, major risk factors that are associated with poor outcomes include comorbidities such as renal failure, diabetes mellitus and hypertension, advanced AIDS and generally unwell clinical status at the time of surgery such as with the case of active endocarditis. Table 2 shows risk factors for mortality and complications. HIV itself does not seem to be independently associated with poor outcomes or operative mortality.[10]

In all these studies, patients that presented for CABG have consistently shown low to absent early mortality in contrast to valve surgery. These patients are generally on ART with stable HIV disease at the time of surgery with good CD4 counts and operated electively. These patients developed coronary artery disease as a result of treatment with ART.

Table 2: Predictors of mortality and complications

Major comorbidity • Renal failure • Diabetes Mellitus • Hypertension
Single or double valve surgery
HIV related disease (2 fold)
Blood transfusions
Liver Dysfunction
Age
Co-infection with hepatitis B/C

We have seen two studies examining large numbers of HIV positive patients who underwent cardiac surgery through data collection using the Nationwide Inpatient Sample (NIS) database.[10, 11] In these studies, HIV was not associated with increased mortality; however, the risk for mortality by CD4 count was not assessed due to unavailability on the NIS database of CD4 counts. If we look at their sub-analysis of mortality and complications, we can use this as proxy for the CD4 count nadir in these patients as follows. When HIV positive patients were stratified according to the presence or absence of Acquired Immunodeficiency Syndrome (AIDS) related conditions, those patients with AIDS-related conditions had increased mortality compare to those without (OR 2.4 95% CI 1.5-3.8 vs OR 1.2 95% CI 0.8-1.8).[10] In addition, HIV positive patients had 16% more increased overall complication risk (OR 1.16 95% CI 1.01-1.34) particularly requirement for blood transfusion.[11] This subgroup of patients may represent those with low CD4 counts with increased mortality and complication rate.

There were no follow-up of patients to determine short or long-term outcomes. In addition, the dependence on coding of by non-medical personnel may have played a

role in over or underestimating certain figures by allocation of diagnoses to incorrect codes.

There have been major gains in the medical care of HIV positive patients since the introduction of ART. There have also been major advances in perioperative management of these patients while there is a downward trend of patients operated presenting with IE. All these factors have contributed in improvement in operative mortality in HIV positive patients.[12, 13]
CABG is becoming the most common cardiac surgery performed in HIV positive in industrialized countries like the United States. Prior to ART, HIV positive patients were rarely addressed to coronary revascularization because of the limited life expectancy.[2] All the studies to date have seen increasing number of patients for coronary revascularization throughout their study periods; there has been excellent outcomes in the long-term in the range of over 80% survival at 3 years. The operative mortality is decreasing with more elective, isolated coronary surgery rather than valve surgery.

Valve surgery in HIV positive patients has historically been associated with IE. However, there is a decreasing trend in the number of patients operated for this indication in industrialized countries. These patients have traditionally had high early mortality rates with only one study showing good outcome with no early mortality.[9] However, we've seen a decrease in the number of patients being operated for IE contributing to reduced early mortality of this patient group over the past decade.

Studies of cardiac surgery in sub-Saharan Africa

There is paucity of research in this topic in SSA with only 3 studies focusing on this population outcomes following cardiac surgery. Blyth et al reviewed 49 patients, average age 33, undergoing various cardiac procedures including CABG, valve replacement, repair of congenital lesions and aortic root surgery.[14] Their criteria for patient entry into surgery was initially good clinical status and subsequently CD4 count above 400 cells/μL. This lead to the average CD4 count in their cohort at 685 cells/ μL.

They reported 6% and 34.7% 30-day mortality and complication rate respectively. Subsequently, Nel et al prospectively studied a cohort of 77 patients with infective endocarditis, with a subset of 17 patients in their cohort HIV positive.[15] The mean age and CD4 count was 30 years and 189 cells/μL respectively. In this study, the morbidity of HIV infected and uninfected patients were similar as were the mortality rate of 23.6% for HIV infected and 23.3% for HIV uninfected patients. Mutyaba et al focusing on pericardial surgery on the largest cohort of 121 showed that perioperative mortality was not influenced by HIV status but New York Heart Association Class IV and hyponatraemia predicted early mortality after pericardiectomy.[16]

In summary, the current literature evidence suggests that HIV does not increase the risk of peri cardiac surgery mortality, and that the outcomes of HIV positive patients undergoing cardiac surgery have improved over the years. CABG is the most commonly performed procedure followed by valve surgery in industrialized countries. Patients with a history of AIDS defining illnesses may be at increased perioperative risk, as are those with renal failure, and anaemia-the latter variables increase risk independent of HIV status. It is still unclear if CD4 count is associated with increased mortality from these studies. Data from Sub-Saharan Africa despite small numbers, is supportive of international trends that mortality of HIV positive patients undergoing cardiac surgery is similar to HIV negative patients.

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SECTION B: Journal Ready Manuscript

The impact of HIV on 30-day survival amongst patients undergoing cardiac surgery at Groote Schuur Hospital in the ART era

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Authorship: The lead investigator Dr L Boloko was responsible for data collection, analysis and interpretation under the supervision of principal investigators, Prof M Ntsekhe, Dr T Pennel and W Basera.

Keywords: cardiac surgery, human immunodeficiency virus

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Abstract

Introduction: Impact of HIV on the one-month perioperative morbidity and mortality in patients undergoing cardiac surgery in Sub-Saharan Africa in the ART era is not known.
Methods: We conducted a retrospective review of the Groote Schuur Hospital patient records between 2003 and 2013. Eighty-one patients met all our study inclusion criteria.
Findings: Mean age was 34, female (73%) and 41% were on ART, 28% had previous tuberculosis and the average CD4 count was 426.5 cells/μL. 54 (67%) underwent valve surgery, 5 (6%) underwent CABG and 3 (4%) had both. 5 (6%) patients died in hospital; the 30-day complication was 23%. The predictors of death included the need for aortic root replacement and prolonged cardiopulmonary bypass time (OR 25 [p=0.006] and OR 1.02 [p=0.01] respectively)
Conclusion: HIV positive patients had cardiac surgical outcomes with low mortality rates comparable to international trends which were independent of CD4 counts.

Word count: 150

INTRODUCTION

Prior to the rollout of antiretroviral therapy (ART) in South Africa, patients infected with human immunodeficiency virus (HIV) were frequently denied cardiac surgery because of concerns about short-term complications, peri-operative infection and the potential risk of infecting healthcare workers. [14, 17] This is despite the lack of evidence to support the perceived presence of increased perioperative mortality or excess risk to health care professionals.[18] The widespread access to ART since 2003, has resulted in significant gains in the adult life expectancy of people living with HIV (PLHIV). Amongst patients starting ART with CD4 T lymphocyte (CD4 count) more than 200 cells/μl, the estimated life expectancy now approaches that of aged matched controls in the general population.[19, 20] As such PLHIV currently have equal access to cardiac surgery but little has been published on their outcome. This is especially important in Africa with the highest burden of disease.

PLHIV may present with a wide spectrum of heart disease which requires cardiac surgical interventions. HIV increases the risk of some but not all these cardiovascular disorders. For example, ART-naïve HIV positive patients have been shown to have an increased risk of myocardial infarction as a result of increased endothelial activation, associated with a pro-inflammatory state and elevated markers of thrombosis. In addition, protease inhibitors may increase the risk of coronary disease as a result of dyslipidemia and other metabolic derangement associated with a clinical phenotype of lipodystrophy.[4, 21-23] Furthermore, with increasing life expectancy as a result ART, an increase in the prevalence of traditional risk factors such as hypertension, diabetes and obesity amongst ART treated HIV positive patients is well described.[24]

Tuberculosis (TB) is responsible for 86% to 100% of pericardial disease in PLHIV and HIV significantly increases the risk of pericarditis. For those with TB pericarditis who progress to develop constrictive pericarditis, the definitive treatment is pericardiectomy.[16, 25] In rheumatic heart disease (RHD) endemic areas of the world, the incidence and prevalence of valvular heart disease and its complications are presumed

to be similar in HIV infected and uninfected hosts, and therefore the need for valve replacement surgery would be similar. Finally, there is also no reason to suspect that the prevalence of undiagnosed congenital heart disease requiring corrective surgery (an important problem in HIV endemic areas such as sub-Saharan Africa) should be any different between PLHIV and uninfected individuals.

Despite the widespread literature on the perioperative outcomes of HIV-positive patients in cardiac and non-cardiac procedures, little is known about HIV associated cardiac surgery particularly in HIV endemic areas.[18, 26, 27] In North American and European studies of patients undergoing cardiac surgery the mortality was shown to range between 0 and 23% with most deaths occurring in those patients operated for infective endocarditis (IE).[2, 7-9] There is paucity of contemporary ART era data from sub-Saharan Africa (SSA) on the experience and outcomes of cardiac surgery in this important population. We undertook this single center retrospective study to address this important information gap.

PATIENTS AND METHODS

This was a retrospective observational study conducted following approval by the Research Ethics committee of the Faculty of Health Sciences of the University of Cape Town (HREC REF: 477/2016). Patients folder numbers were obtained from a surgical database (HREC REF: R044/2016) at the Chris Barnard Division of Cardiothoracic Surgery, Groote Schuur Hospital, South Africa between 2003 and 2013. Folder numbers were cross referenced against the National Health Laboratory Services to identify HIV positive patients. For each patient who met inclusion criteria, information on demographics, comorbidity, special investigations, clinical parameters including New York Heart Association (NYHA) level of dyspnea and outcomes were captured. Relevant data was collected from the medical records into a pre-specified datasheet and transferred onto REDCap data management tool. Only complete records were considered for analysis.

Outcomes

The primary outcomes of interest included in-patient mortality and 30 day morbidity. The secondary outcomes included NYHA functional class at 30 days' follow-up, length of stay and causes of death.

Covariables

Other clinical variables collected included preoperative NYHA functional class, anthropometry, echocardiographic findings, and patient ART history. Surgical procedures were categorized as coronary artery bypass graft (CABG), valve repair or replacement, aortic root repair or replacement, or a combination of these and pericardiectomy. Other cardiac procedures included were repairs of congenital lesions.

Statistical analysis

All statistical analyses were performed using Stata/SE 15.1. Statistical tests were performed according to whether the variable is continuous or categorical. Continuous data were expressed as mean values ± SD or median values (IQR) depending on the normality of data. Categorical data comparisons were performed with χ_2 or Fisher exact test were used to test for a statistical difference between variables. To further study associations we performed stepwise multivariate analysis using logistic regression for categorical and continuous variables.

RESULTS

Patient characteristics

A total of 3395 patients were recorded to have been operated in the period of the study, and of those, 109 were confirmed HIV positive. Complete medical records of 81 participants were obtained and captured for analysis.

Figure 1. Flow diagram showing patient inclusion

The median CD_4 count was 426.5 cells/μL (126-1402); thirty-three (40.7%) patients were on ART perioperatively with 25 (30.9%) patients having had the acquired immunodeficiency syndrome (AIDS) defining conditions (e.g. TB and *pneumocystis jiroveii pneumonia* (PJP)) previously. Only one patient was HIV and hepatitis B co-infected. The patients were predominantly black (n=67; 82.7%), median age 34.3±10.9 and female (n=59; 72.8%) as listed in Table 1. The majority of patients were considered to be normal weight for height (n=40; 55.6%) with just over a quarter in the overweight category (n=20; 27.8%). Only one patient had chronic kidney disease with eGFR <30; the median haemoglobin was 11.8±2.2; INR 1.3±0.36; creatinine 74±36.3.

Table 1. Demographic characteristics and special investigation

The comorbid conditions are shown in Table 2.
A majority of the patients were in heart failure (n=65; 80.2%) at the time of surgery and documented RHD was present in 41 (50.6%) patients. The disease process was complicated by atrial fibrillation (n=17; 21%) in a subset of patients; pulmonary hypertension in 25 (30.9%) while 13 (16%) patients were smokers. Nine (11.1%) patients were diagnosed with IE in the perioperative period with 6 (7.4%) having had a distant history of previous IE. Of the 3 (3.7%) patients with previous ST elevation myocardial infarction, one was as result of vegetation embolus to epicardial coronary vessels. Tuberculosis (n = 23; 28.4%) was the most common opportunistic infection previously documented, also representing the only cause of constrictive pericarditis requiring pericardiectomy in this population.

Table 2. Preoperative comorbidities

There were 24 (29.6%) patients with severe aortic regurgitation on echocardiographic examination, 13 (16%) patients had severe mitral stenosis, 18 (22.2%) patients had severe mitral regurgitation, and the mean left ventricular ejection fraction was 54.3±12. Twenty (24.7%) patients required urgent surgery while emergency surgery was done in 3 (3.7%). All emergency surgeries were redo MVR for stuck valve prosthesis; there

were 7 (8.6%) patients with prosthesis thrombosis, all secondary to anticoagulation non-compliance.

The mean Euroscore was 3.6±4.6. The distribution of surgeries performed are shown in Figure 2 below. The majority of patients had valve replacement; ten (12.4%) patients had pericardiectomy, while AVR (n= 17; 21%) was the most predominant valve surgery done; of the AVR patients 15 (88.2%) had mechanical prosthesis and 2 (11.8%) had bioprosthesis. Sixteen (19.8%) patients had MVR; mechanical prosthesis (n=14; 87.5%) and bioprosthesis (n= 2; 12.5%). Twelve (14.8%) patients had double valve replacements. Only 4 (4.9%) had CABG, of these 2 (2.5%) for were atherosclerosis related coronary artery disease.

Figure 2: Type of surgery performed

Findings

The outcomes of HIV positive patients undergoing cardiac surgery are presented in Table 3.

A total of 5 (6.2%) patients died in-hospital postoperatively with no intraoperative deaths. The 30 day post-operative morbidity rate was 23.5%. The recorded morbidities included the need for blood transfusion (n=16; 19.8%), bleeding (n=14; 17.3%), sternal wound sepsis (n=9; 11.1%), pleural effusions (n=7; 9%), atelectasis (n=5; 6.2%) and complete heart block (n=5; 6.2%). Two (2.5%) patients required repeat surgery, one thoracotomy for a clotted haemothorax, another had sternotomy for ongoing bleeding and blood loss. Three patients (3.7%) had a postoperative cardiac tamponade requiring drainage via a subxiphoid window.

With regards to the secondary outcomes, freedom from dyspnea at 30 days was seen in 61 (87.1%) patients at NYHA class I (n=5; 6.2% at baseline), 9 (12.9%) patients at NYHA class II (n=23; 28.4% at baseline) and no patient remained at NYHA class III (n=36; 44.4% at baseline) and NYHA class IV (n=17; 21% at baseline). Patients with advanced heart failure (NYHA class III/IV) preoperatively attained significant freedom from dyspnea at 30-days of follow-up ($p < 0.001$). The median length of stay was 25.8

days and the main causes of death were mainly cardiac failure in 2 (2.5%) patients and sepsis in 3 (3.7%) patients.

Of the participants who died from sepsis one was operated electively for *H. Influenzae* endocarditis and demised following prolonged ischemia for a combined aortic root replacement, MVR and CABG; this patient had extensive subacute bacterial endocarditis involving coronary ostia. The second patient developed *S. Aureus* sepsis following urgent aortic root reconstruction, and the third following urgent AVR for endocarditis. Cardiac failure was implicated in a patient with post cardiotomy low cardiac output syndrome who required intra-aortic balloon pump with high dose ionotropic support. There was no in-hospital mortality in patients undergoing pericardiectomy.

By univariate analysis the following variables were associated with in-hospital mortality: aortic root replacement, redo AVR, culture positive endocarditis and atrial flutter. Multivariate analysis showed that cardiopulmonary bypass duration (OR 1.02 CI 1-1.04; p 0.01) and aortic root replacement surgery (OR 25 CI 2.5-239; p 0.006) were predictive of in-hospital mortality. There was no association between CD4 count and in-patient mortality.

We did not find any association between CD4 count and the occurrence of any complications. Aortic root disease and prolonged hospital stay were associated with bleeding while aortic valve disease, acute kidney injury and prolonged hospital stay were associated with increased risk of the need for blood transfusions; patients with previous cardiac surgery, redo AVR, prolonged hospital stay and male sex were likely to develop acute kidney injury. There was only one (1.2%) reported needle-stick injury to the operating surgeon. There were no reported thromboembolic disease or urinary tract infections. No patient required pre or postoperative dialysis. The loss to follow-up rate was 7.4% with 5.3% of those patients included into those that were transferred to their referring hospital and subsequently followed up there.

Table 3. Post-operative outcome

DISCUSSION

This study investigated the 30-day survival and morbid outcomes of HIV positive patients undergoing cardiac surgery. The main findings were that the 30-day post-operative mortality was 6.2% and the perioperative complication rate was 23.5%. Other important findings included that the vast majority of patients obtained relief from dyspnea at 30 days.

The first study of this kind in SSA reported by Blyth et al described hospital mortality and complications rates of 6% and 34.7% respectively for HIV positive patients.[14] In the same centre as Blyth, a smaller subgroup of HIV positive patients were found to have a mortality of 23% over a 3 year period, however no early mortality.[15] Although the current complication rate is lower than previously described, we had expected an even lower figure given advances in general medical and surgical care as well as use of ART. Nevertheless, we did not find any relationship between any of the outcomes and CD4 count; this resonates with previous literature describing similar outcomes in HIV positive and non-HIV positive patients regardless of the site of surgery, except anorectal surgery.[27]

Previous studies have shown that a history of stroke, diabetes mellitus, congestive heart failure, impaired left ventricular function, previous cardiac surgery, age and beta blocker use were common in those with major morbidity and operative mortality. This was not evident in this current study and may be partly explained by the younger patient population (mean age less than 40) and the absence of major comorbidities. In addition, high preoperative creatinine, a lower eGFR, a longer cardiopulmonary bypass duration, longer cross-clamping and longer hospitalization stay contribute to morbidity and mortality.[10, 28] In this study we found that a cardiopulmonary bypass duration and aortic root replacement were statistically significantly associated with in-hospital mortality.

There was no intra or postoperative mortality in patients undergoing pericardiectomy. Several recent studies found a pericardiectomy mortality rates of 14-17.6%.[11, 16] Only 12.3% of our cohort underwent pericardiectomy despite a high burden of TB pericarditis,

an observation that may be related to the lower incidence of pericardial constriction previously described in HIV positive patients.[29]

Less than 50% of patients were on ART in this cohort. This may partly be explained by the national treatment policy up to 2010 was that patients were only eligible for treatment once CD4 count fell below 200 cells/μl or patient had clinical stage IV as defined by the World Health Organization (DoH 2003).[30] The median CD4 count was 426.5 cells/μl whether this reflects previous practice of only selecting patients with an absolute CD4 cell count above 400 cells/μL for elective cardiac surgery[14] or is a coincidental finding is not known. Our study overlapped with a period of concerted effort to increase countrywide rollout of ART in South Africa as evidence by a significant jump in ART coverage from 47500 in 2004 to 1.79 million in 2011.[31]

Only 5% of patients undergoing surgery had a CABG; a small minority of the patients had traditional risk factors for atherosclerosis and only 4% of the cohort were on a PI. First-line ART regimens in South Africa over the period of the study were nucleoside reverse transcriptase and non-nucleoside reverse transcriptase inhibitors based[32] explaining why so few were using PIs.

RHD was the most common cause for valvular heart disease (51%). The prevalence of RHD in South Africa has previously been reported to be 20.2 cases per 1000 children based on single study.[33] Infective endocarditis was the indication for surgery in 18.5% of patients. Koegelenberg et al did not find HIV to be a risk factor for IE in the Western Cape.[34] In the patients with active endocarditis, 3.7% were culture positive while 7% were culture negative. The incidence of culture negative endocarditis may reflect antibiotic administration prior to sampling of blood cultures as this is the most common cause of culture negative endocarditis.[15, 35]

The majority of patients with valve replacement surgery received mechanical valves for both mitral and aortic prosthesis; these patients were younger than 60 years of age as per European Society of Cardiology guidelines.[36] Although mechanical valves offer

longer durability, they are associated with anticoagulation-related bleeding and thromboembolism. All emergency surgeries done in this cohort were for stuck valves related to warfarin non-compliance. In addition, the median length of stay was 25.8 days with time to therapeutic international normalized ratio (INR) for warfarin a major contributor while in those patients with endocarditis, antibiotics duration before surgery was another contributor.

In conclusion, this retrospective single center study suggests that in an era in which the population coverage of ART amongst HIV infected patients is approximately 50%, the perioperative mortality and morbidity is in line with what has been described in other parts of the globe but has changed little over the last decade in South Africa. The data suggests that over the period covered by the review few patients with advanced HIV were being selected for cardiac surgery.

Our study has several limitations, firstly this is a single centre experience and cannot be generalized to the heterogenous practice in the resource limited sub-Saharan region. Secondly, the retrospective nature of the study made it difficult to find all patients with complete data reducing the study population and ability to study certain associations. Third, we did not have a control group to make comparisons to HIV uninfected population. Lastly, this patient population may represent a carefully selected HIV positive patient undergoing cardiac surgery as determined by previous practices dictating that patients should not undergo cardiac surgery if CD4 count less than 400 cells/μL.

Acknowledgements

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FIGURES AND TABLES

Figure 1. Flow diagram showing patient inclusion

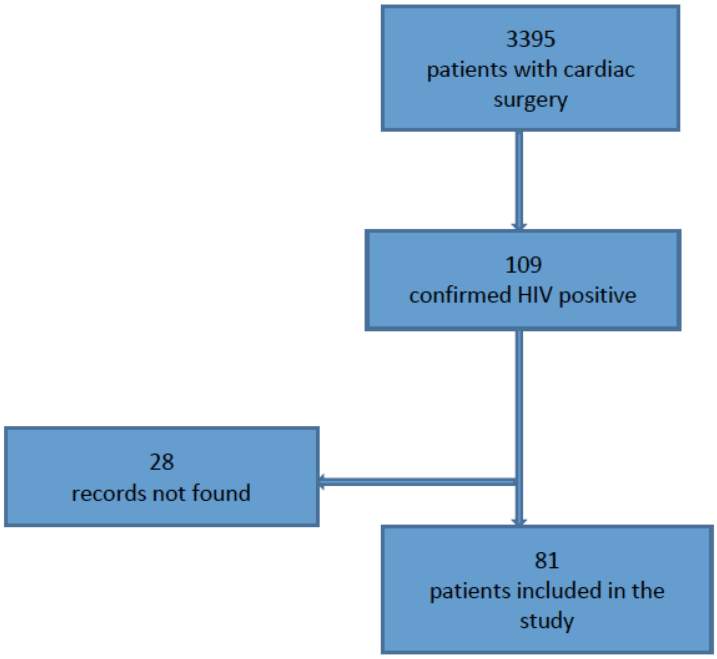

Figure 2. Type of surgery performed

Characteristic	HIV n=81, (%)
Median age , y ± SD	34.3 ± 10.9
Age group	
0-29	28 (35)
30-39	31 (38)
40-59	21 (26)
Female	59 (72.8)
Anthropometry	
Normal	40 (55.6)
Overweight	20 (27.8)
Race	
Black	67 (82.7)
Colored	11 (13.9)
White	3 (3.7)
Special investigations	Median ± SD (min-max)
Haemoglobin	11.8 ±2.2 (7-19)
Creatinine	74 ± 36.3 (43-286)
eGFR	106.1 ± 25.6 (21-130)
INR	1.3 ± 0.36 (1-3.3)
LVEF by echocardiogram	54.5 ± 12 (27-83)

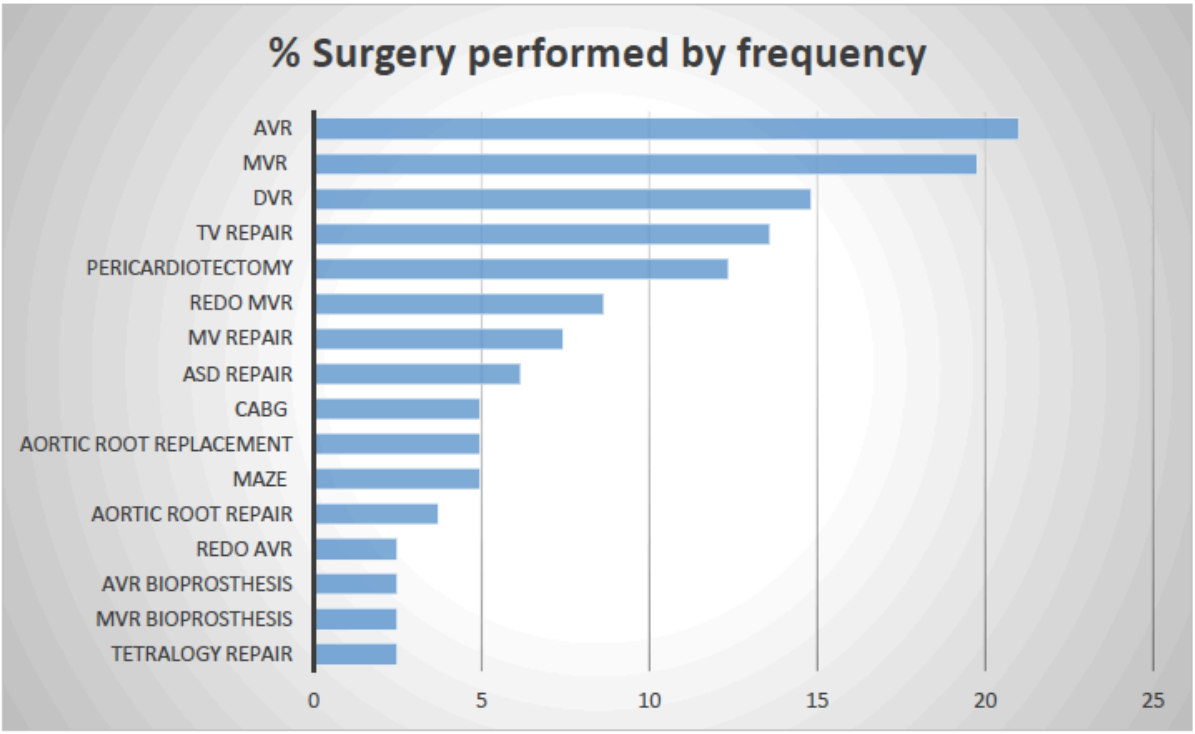

Table 1. Baseline demographic characteristics and special investigations

Table 2. Pre-operative comorbidities

Characteristics	HIV n = 81, (%)
Hypertension	6 (7.4)
Heart Failure	65 (80.2)

Diabetes Mellitus	1 (1.2)
Rheumatic heart disease	41 (50.6)
Previous Stroke	5 (6.2)
Smoking	13 (16)
Chronic kidney disease	1 (1.2)
Cardiomyopathy	2 (2.5)
Previous Tuberculosis	23 (28.4)
COPD	4 (4.9)
Previous Endocarditis	6 (7.4)
Active endocarditis	9 (11.1)
Previous PCP	1 (1.2)
Dyslipidaemia	3 (3.7)
Unstable angina	2 (2.5)
NSTEMI	2 (2.5)
STEMI	3 (3.7)
Hepatits B	1 (1.2)
Congenital Aortic Disease	2 (2.5)
Degenerative AV disease	2 (2.5)
Atrial fibrillation	17 (21)
Atrial flutter	3 (3.7)

Table 3. Post-operative outcomes

Event	n(%)
Hospital mortality n, %	5 (6.2)

Functional class at 30 days n, %	
New York Heart Association I	61 (87)
New York Heart Association II	9 (12.8)
Complications n, %	19 (23.5)
Wound sepsis	9 (11.1)
Pneumonia	3 (3.7)
Complete heart block	5 (6.2)
Bleeding	14 (17.3)
Acute kidney injury	4 (4.9)
Haemothorax	1 (1.2)
Atelectasis	5 (6.2)
Stroke	1 (1.2)
Pleural effusion	7 (8.6)
Atrial fibrillation	1 (1.2)
Atrial flutter	2 (2.5)
Cardiac tamponade	3 (3.7)
Repeat thoracotomy	2 (2.5)
Blood transfusion	16 (19.8)
Pneumothorax	1 (1.2)
Pneumopericardium	1 (1.2)
Needle-stick injury	1 (1.2)
Discharge disposition, n (%)	
Home	72 (94.7)
Transfer base hospital	4 (5.3)
Length of hospital stay, median d	25.8 (6-116)
30 days' follow-up n, %	
Alive	70 (86.4)
Died	5 (6.2)
Loss to follow-up	6 (7.4)

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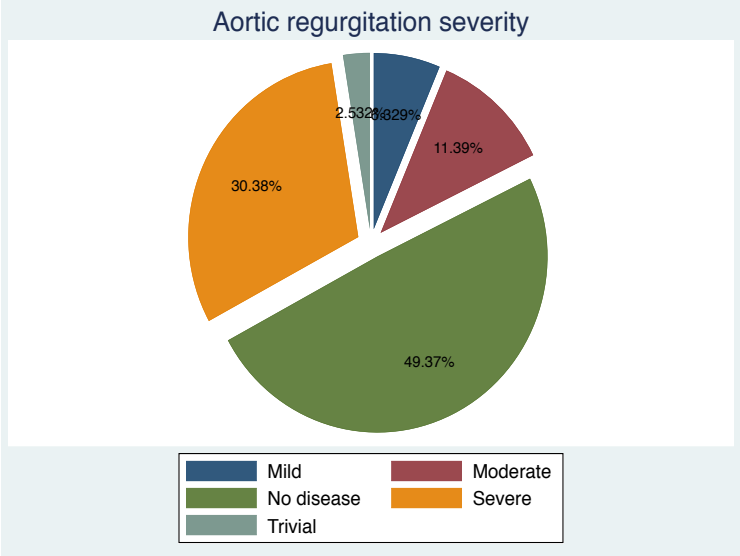
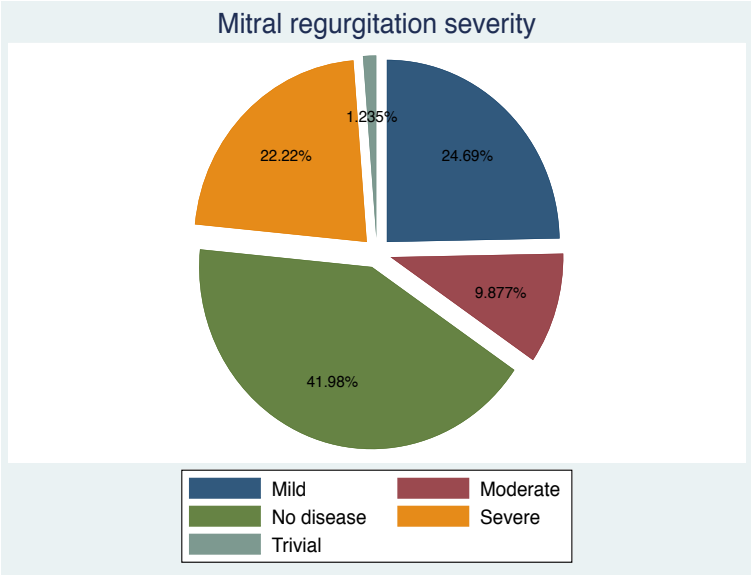
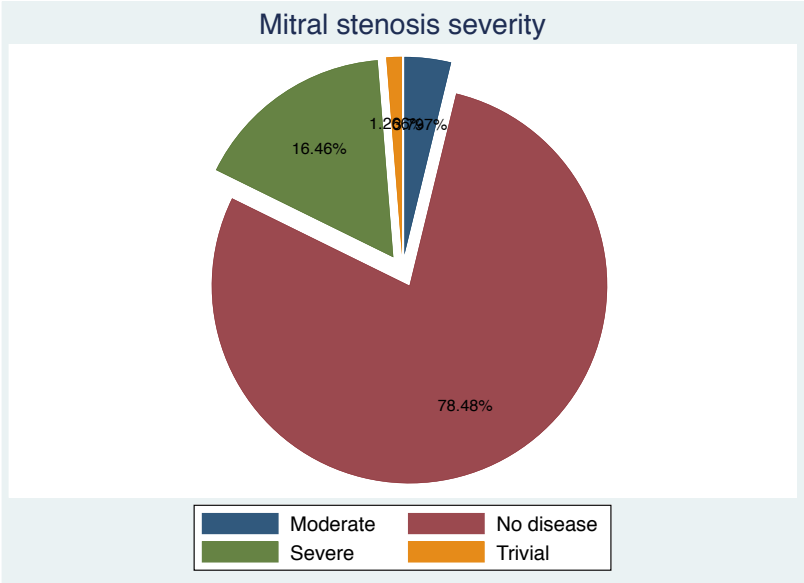
APPENDICES

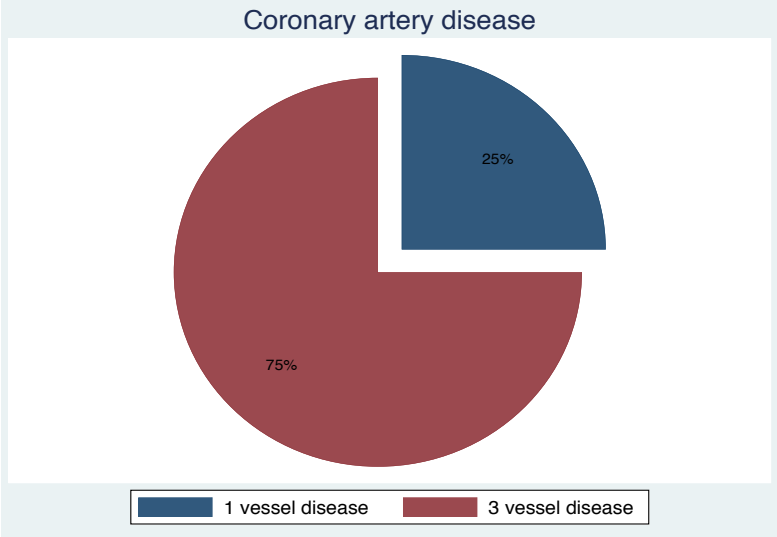
Appendix 1. Additional figures

Cardiac lesions



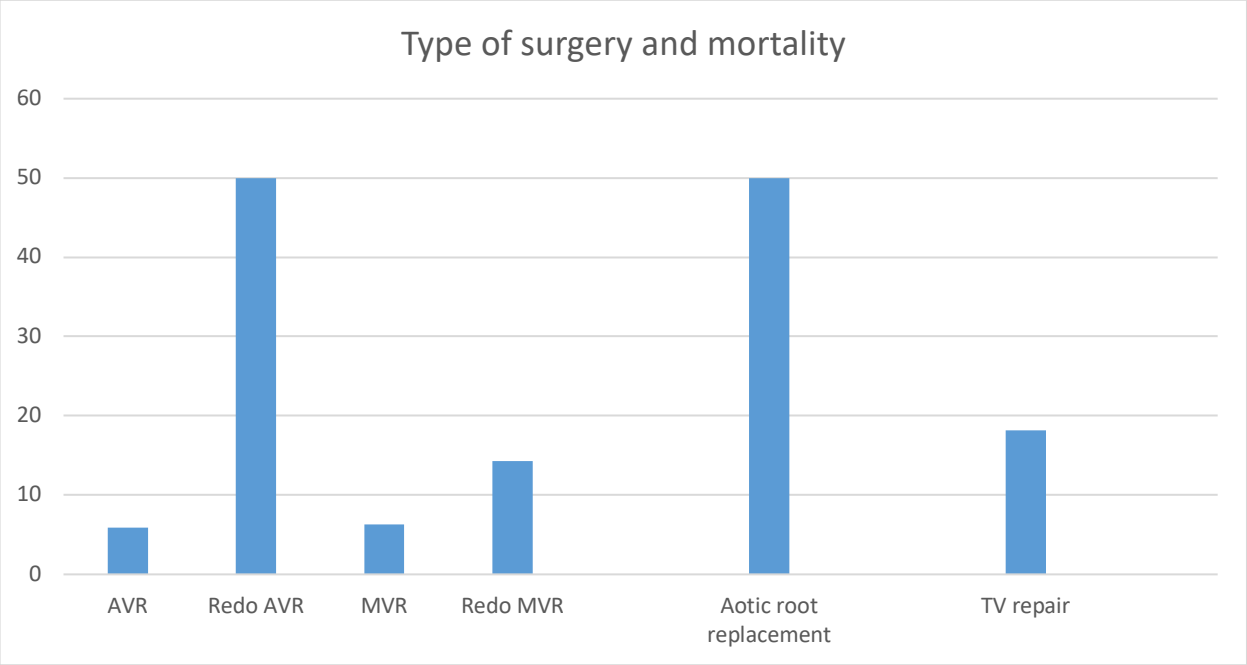






Severity of cardiac lesions in the studied population

Mortality and surgery



Redo AVR and aortic root replacement associated with increased mortality ($p < 0.001$)

Appendix 2. Additional tables

Effect of CD4 count on mortality	
Median CD4 count - Alive	428 (272 - 628)
Median CD4 count - Dead	519 (300 - 659)
Median CD4 count - LTFU	413 (401 - 480)

CD4 count appears to be higher in those who die compared to the other categories, however the difference is not significant (p 0.85)

HIV immune status	
Median CD4 count (15th, 85th percentiles)	426.5 (272, 628)
ART preoperative	33 (40.74)
NRTI	33 (40.74)
NNRTI	33 (40.74)
PI	3 (3.7)
Previous AIDS defining	25 (30.86)

Level of dyspnea	
Proportion with NYHA III/IV pre-op	53 (65.4)
Proportion with NYHA I at 30 days	35 (66.0)

A significant proportion of those who start with dyspnea at pre-op attain freedom at 30 day follow-up (p <0.001)

Surgical characteristics	
Euroscore	
Mean +- SD	3.58 +-4.63
Min	0,5
Max	25,71
AVR n, %	
Bioprosthetic	2 (2.47)
Mechanical	15 (18.52)
MVR n, %	
Bioprosthetic	2 (2.47)
Metallic	14 (17.28)
TV repair n, %	11 (13.58)
Aortic root replacement n, %	4 (4.94)
Aortic root repair n, %	3 (3.7)
CABG 1 n, %	1 (1.23)
CABG 3 n, %	2 (2.47)
CABG 4 n, %	1 (1.23)
ASD repair	5 (6.17)
Pericardectomy	10 (12.35)
MAZE procedure	4 (4.94)
TOF repair	2 (2.47)
Redo-MVR	7 (8.64)
Redo-AVR	2 (2.47)
DVR	12 (14.81)
MV repair	6 (7.41)
Emergency surgery	3 (3.7)
Urgent surgery	20 (24.69)
Aortic clamp time	
Mean +- SD	81.6 +-60.58
Min	0
Max	285
Cardiopulmonary bypass	
Mean +- SD	122.24 +-85
Min	0
Max	300

Appendix 3. Data collection sheet

The impact of HIV on one-month survival amongst patients undergoing cardiac surgery at Groote Schuur Hospital in the ART era

Demographics

Surname					
First name					
Date of birth (dd-mm-yyyy)					
Sex	Male	Female			
Race if available	African Black	Colored/mixed-ancestry	White	Indian/Asian	Other

Immune status

HIV Status		Positive			Negative		
Year of diagnosis		Prev. AIDS-defining condition	Y	N	CD4 count (cells/μL)		
VL perioperative(copies/mL)		ART perioperative	Y	N	NRTI	NNRTI	PI	Other
Time on ART		<3 mo	3-6 mo	6-12 mo	>12 mo		
Compliance on history		Yes	No				

Comorbidities

HPT	Diabetes Mellitus	Insulin use	Previous stroke	Smoking	COPD	
CKD	Rheumatic Fever	Cardiomyopathy	Atrial fibrillation	Previous Tuberculosis		
Asthma	Anaemia	Peripheral vascular disease	Chronic lung disease			
Recent MI (90 days)	Rheumatic heart disease	Heart failure	Dyslipidemia	Unstable Angina	Stable Angina	
Prev. NSTEMI	Prev. STEMI	Liver Disease	Pulmonary hypertension	Rheumatoid Arthritis	Hepatitis B	Hepatitis C
SLE	Hypothyroidism	Hyperthyroidism	Coagulopathy	Lymphoma	Prev. cancer	Large vessel vasculitis

Biochemical

Hb		Creatinine		eGFR		Triglyceride		Cholesterol		LDL	
HDL		INR		Tot. Bili		Albumin					

Cardiac status pre-op

1 vessel disease	2 vessel disease	3 vessel disease	Ejection Fraction		Mitral valve disease	Aortic valve disease	Pulmonary valve disease	Tricuspid valve disease
Previous PCI	Angioplasty	Prev. DES	Prev. BMS			Previous cardiac surgery (n)		Pericardial disease
NYHA I	NYHA II	NYHA III	NYHA IV	CCS I	CCS II	CCS III	CCS IV	
Weight (kg)		Height (cm)		BMI		mPAP (mmHg)		
Mitral regurgitation		Trivial	Mild		Moderate		Severe	

Aortic regurgitation	Trivial	Mild	Moderate	Severe
Tricuspid regurgitation	Trivial	Mild	Moderate	Severe
Mitral stenosis	Trivial	Mild	Moderate	Severe
Aortic stenosis	Trivial	Mild	Moderate	Severe
Ionotropic support	Ventilation	Dialysis	IABP	ICU admission
Active Endocarditis	Culture positive	Culture negative		
Organism		Aortic disease		

Perioperative

AVR	MVR	TVR	AVR-MVR	AVR-MVR-*tricuspid repair*	MV Repair
MVR-*tricuspid repair*	AVR-*mitral repair*	Tricuspid repair	Aortic root replacement	CABG 4	Emergency surgery
CABG 1	CABG 2	CABG 3	Urgent surgery	Elective surgery	Mechanical valve
Bioprosthetic valve	Aortic Clamp time (*min*)		Cardiopulmonary bypass (*min*)		Pericardectomy
Re-do MVR	Re-do AVR	TOF repair			
Year of surgery		EuroScore II		STS score	

Postoperative morbidity

Sternal wound sepsis	HAP	Mediastinitis	UTI	Complete Heart Block	Tamponade	Bleeding
Thromboembolism	AKI	Line sepsis	Dialysis	Atelectasis	Pleural effusion	Stroke
Prolonged Ventilation (days)		Ventricular Fibrillation	Ventricular Tachycardia	Atrial Fibrillation	Leg/arm wound sepsis	Blood transfusion
Coagulopathy	IABP	LVAD use	Pneumopericardium	Pneumothorax		

Mortality and follow-up

Total hospital stay (days)		Hospital stay post-op		
Date of admission		Date of death		
Discharge disposition	Home	Inpatient care	Transfer base hospital	
Follow-up disposition at 30 days	Alive	Dead	Loss to follow-up	Hospitalized
NYHA at 30 days	NYHA I	NYHA II	NYHA III	NYHA IV
CCS at 30 days	CCS I	CCS II	CCS III	CCS IV
Time from surgery to death (days)				
Cause of Death				